REMARKS

Claims 15 and 31-35 are pending. The amendments to claim 15 are supported by canceled claims 27 and the published application at [0012]

Claims 15, 17-20, 22, 24, 26, 28 and 30-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura et al. in view of Postma et al. (Office Action, Page 2)

Claims 17-20, 22, 24, 26, 28 and 30 are canceled making the rejection with respect to these claims moot.

As for the combination of Kimura and Postma, the applicants respectfully rebut the rejection as follows:

First, it was indicated that Aoki et al. discloses that inflammatory cellular infiltration, including pulmonary eosinophilia, is decreased more by TA-270 relative to theophylline (Table 1, p.328), and therefore TA270 and theophylline do not have the same level of anti-inflammatory effect. However, **Aoki et al.** does not disclose the evaluation data of theophylline. Thus the understanding is not accurate.

As mentioned in the July 30, 2008 response, neutrophil is the main inflammatory cell for COPD (see Global initiative for chronic Obstructive Lung Disease (GOLD), Global guideline for COPD). Thus, even if TA-270 exhibits its effect on eosinophilia in asthma guinea pigs, it does not mean the treatment of COPD.

The therapeutic agent that has currently been used in clinical practice is mostly a bronchodilator. Among the therapeutic agents, the agent that also has anti-inflammation effect is theophylline. However, TA-270 is not considered to be a bronchodilator. In the July 16, 2008 Declaration, theophylline, which was selected in view of the above background, was used for showing a comparative result in the pulmonary emphysema model (induced by cigarette smoke solution (CSS) + lipo-polysaccharide from E. coli (LPS)).

As a result, in the evaluation on "airway resistance," TA-270 exhibited the same level of improvement with theophylline having bronchodilator activity (Fig. 3). ***Further, surprisingly, in the evaluation on "residual volume," TA-270 exhibited an improvement that even theophylline, which has been used in clinical practice due to its bronchodilator activity and anti-inflammation effect, did not exhibit.*** As such, TA-270 is shown to have an unexpected effect to a skilled person in the art.

Second, it was indicated that TA-270 and theophylline were not evaluated against COPD guinea pig model since the guinea pigs were treated with TA-270 or theophylline *before* actual development of the pulmonary emphysema.

In this field, a skilled person usually evaluates the therapeutic effect of test compound by administering them concurrently or before the developing process of disease. There are several references showing this fact. **Bos et al.**, enclosed, discloses that guinea pigs were challenged with ovalbumin (OVA) *once weekly, for 12 consecutive weeks,* to induce airway remodeling (see <Study design> at page 654). For the evaluation on airway remodeling, the guinea pigs received tiotropium (bronchodilator; therapeutic agent for COPD) or budesonide (commercial steroid) 30 min or 24 and 1 h *prior to* each challenge. **Aharony**, enclosed, discloses that zafirlukast (anti-asthma agent) was administered to guinea pigs 30 min *before* LTD_4 challenge (see <Animal models> at page S216). **Mizutani et al.**, which was cited in the rejection, also discloses that to evaluate the effect of theophylline on COPD, theophylline was administered once a day, 1h *before* the respective instillations of CSS or LPS on days 0–18 (CSS + LPS + theophylline group) (see <Study Design> at page 1560).

In the Declaration, cigarette smoke solution (CSS), which was prepared by bubbling a stream of the smoke into saline and is specified as an risk factor for COPD in the GOLD (Global guideline for COPD), and lipo-polysaccharide from E. coli (LPS), which is nonspecific inflammation inducing material, were used as airway inflammation inducing material. While one could be concerned about inactivation of the inducing material (CSS + LPS) by directly reacting with the test compound before the development of COPD during the parallel co-administration; in this case, airway inflammation would not be induced and as a result, COPD model could not be established.

However, the applicants believe that the inactivation of the inducing material does not occur, even in such case, in view of several reasons including.

First, in the July 16, 2008 Declaration, the airway inflammation inducing materials (CSS + LPS) were *intratracheally* administered directly into the airway and the test compound was *orally* administered directly into digestive tract. It is hardly believable that all of CSS and LPS intratracheally administered is inactivated by the test compound orally administered.

Second, since the pharmacological effects of the test compound are anti-oxidation and leukotriene biosynthesis inhibition, the test compound can not inactivate CSS and LPS directly. Since the pharmacological effect of theophylline, a commercial drug, is phosphodiesterase inhibition, even theophylline can not inactivate CSS and LPS directly.

The pharmacological evaluation of the Declaration shows that the accumulation or the activation of the inflammatory cells into airway and the following increase of airway tissue obstruction induced by CSS and LPS can be suppressed by the anti-oxidation and leukotriene biosynthesis inhibition of the test compound. Thus, one could evaluate that the test compound suppresses the airway inflammation or deteriorating disease.

Furthermore, if the test compound inactivates CSS directly, it can be said that the test compound is an useful therapeutic agent considering that cigarette smoke has been known as a main risk factor for COPD and the airway inflammation induced by CSS was suppressed by the test compound.

Accordingly, as demonstrated, it is possible to evaluate the improvement or suppression effect on COPD from the experiment data obtained by administering the test compound to the COPD model induced by CSS and LPS by using the parallel co-administration method. The guinea pig model in the Declaration is COPD model having actual development of the pulmonary emphysema.

As mentioned above, while TA-270 exhibits the same level of improvement with theophylline in the evaluation on "airway resistance," ***TA-270 exhibits an improvement that even theophylline does not exhibit in the evaluation on "residual volume" which is a significant factor in COPD (see Dykstra et al. previously filed).*** TA-270 has in fact an unexpected effect.

As a result of the above showing of unexpected effects over Kimura in view of Postma, claim 15 and its dependent claims are not obvious to a skilled person in the art over the cited references.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

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Encl:

Bos et al., "Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: a comparison" Eur. Respir. J. 2007; 30:653-661.

Aharony, David, "Pharmacology of Leukotriene Receptor Antagonists," Am J Respir Crit Care Med. Vol. 157, ppS214-S219.